

# Cancer Mortality After Nasopharyngeal Radium Irradiation in The Netherlands: a Cohort Study

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**Background:** Nasopharyngeal radium irradiation (NRI) was used widely from 1940 through 1970 to treat otitis serosa in children and barotrauma in airmen and submariners. We assessed whether NRI-exposed individuals were at higher risk for cancer-related deaths than were nonexposed individuals. **Methods:** We conducted a retrospective cohort study of all-cause and cancer-related mortality in 5358 NRI-exposed subjects and in 5265 frequency-matched nonexposed subjects, who as children were treated at nine ear, nose, and throat clinics in The Netherlands from 1945 through 1981. We recorded personal and medical data from original patient medical records and assessed vital status through follow-up at municipal population registries. Risk of mortality was evaluated by standardized mortality ratios (SMRs). All statistical tests were two-sided. **Results:** The average radiation doses were 275, 10.9, 1.8, and 1.5 cGy for the nasopharynx, pituitary, brain, and thyroid, respectively. The median follow-up was 31.6 years. Three hundred two NRI-exposed subjects had died, with 269.2 deaths expected (SMR = 1.1; 95% confidence interval [CI] = 1.0 to 1.3); among nonexposed subjects, 315 died, with 283.5 deaths expected (SMR = 1.1; 95% CI = 0.99 to 1.2). Cancer-related deaths of 96 exposed subjects (SMR = 1.2; 95% CI = 0.95 to 1.4) and 87 nonexposed subjects (SMR = 1.0; 95% CI = 0.8 to 1.3) were documented. There were no excess deaths from cancers of the head and neck area among exposed subjects. However, there were excess deaths from cancers of lymphoproliferative and hematopoietic origin (SMR = 1.9; 95% CI = 1.1 to 3.0), mainly from non-Hodgkin's lymphoma (SMR = 2.6; 95% CI = 1.0 to 5.3). We found no evidence that breast cancer deaths were less than expected (SMR = 1.7; 95% CI = 0.9 to 2.8) in contrast to an earlier

study. **Conclusions:** Our findings do not indicate an increased cancer mortality risk in a population exposed to NRI in childhood. More prolonged follow-up of this and other NRI cohorts is recommended. [J Natl Cancer Inst 2001;93:1021-7]

From the early 1940s until the mid-1960s, nasopharyngeal radium irradiation (NRI) was considered to be an effective therapy for childhood eustachian tube dysfunction (secretory otitis media) (1,2). In the United States, NRI was also applied to aviators and submariners with middle-ear barotrauma (3,4). Both disorders are characterized by lymphoid tissue hyperplasia in the nasopharynx. NRI therapy involved inserting a radium-containing cylinder through the nostril into the nasopharyngeal cavity, close to the tubal orifice, which effectively shrank the lymphoid tissue in that area (5). High radiation doses (i.e., up to several grays) were delivered to the nasopharyngeal cavity, whereas other tissues in the head and neck area, such as the thyroid gland, salivary glands, and brain, received low doses of radiation (i.e., <30 cGy) (6). At least 8000 servicemen and as many as 2.5 million civilians may have been treated with NRI in the United States (7,8). NRI therapy was also reported in Canada (8) and in several European countries (8,9), including The Netherlands, where at least 24 500 patients were estimated to have been treated (9). NRI therapy was abolished gradually because it was acknowledged that radium treatment might cause adverse late health effects (10), and new effective forms of therapy for secretory otitis media were introduced.

Several cohort studies (11-13) have addressed the long-term cancer risks in children treated with NRI. In addition, Kang et al. (14) studied mortality among military personnel who were treated with NRI, but such studies (15,16) are difficult to conduct because military medical records are often no longer accessible. Because of the small sample sizes and relatively short follow-up periods in all studies, results regarding NRI-associated cancer risk so far have been inconclusive. However, there has been public concern and scientific controversy over a possible increased risk of brain tumors in NRI-treated individuals (17-19). A 1995 workshop (20) addressing "the public health response to NRI" resulted in recommendations for additional research into the

late health effects among NRI-treated populations, including extending the follow-up period of existing cohorts and paying more attention to cancer end points.

In this report, we present the overall and cause-specific mortality results after a prolonged follow-up of a Dutch cohort of patients treated with NRI. We focused on cancers of the head and neck area and of lymphoproliferative and hematopoietic origin. In addition, because radiation damage to the pituitary gland has been hypothesized to reduce the risk of hormone-dependent cancers (21), we also focused on cancers of hormone-dependent tissues, including the breast, the female genital tract, and the prostate gland.

## SUBJECTS AND METHODS

### Study Population

In 1982, a cohort of 2547 NRI-exposed subjects treated previously with NRI from 1945 through 1965 was identified from patient medical records from the ear, nose, and throat (ENT) departments of five clinics in The Netherlands. A frequency-matched nonexposed subject group of 2381 ENT patients who were not treated with NRI was identified on the basis of clinic, sex, year of birth, and year of first consultation. Further details on the original cohort have been described previously (13). For this study, the cohort was expanded to include additional Dutch subjects who had received NRI treatments from 1945 through 1981. The additional NRI-exposed subjects were identified from medical records of ENT departments in three clinics that had not participated in the previous study (13) and in two clinics that had already participated. NRI-exposed subjects were grouped by sex, date of birth, and date of first radiation treatment (5-year periods). Nonexposed subjects were selected from the patient rosters in the same clinics. To avoid selection bias, all units (i.e., boxes or drawers) of the medical records were assigned a rank number, and tables of random num-

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bers were used to select units that were searched until a matched nonexposed subject was found for each NRI-exposed subject. We added 2845 NRI-exposed subjects and 2920 matched nonexposed subjects to the original cohort, for a total of 5392 NRI-exposed subjects and 5301 nonexposed subjects.

For one clinic, we could not find sufficient numbers of records to frequency match NRI-exposed and nonexposed subjects for the expanded search. Therefore, we selected 90 nonexposed subjects from another hospital in the same region. NRI-treated subjects from one of the three new participating clinics were included in this study by restricting their person-year experience and deaths to the period from 1982 through 1997, since data were incomplete for the earlier years.

Institutional review boards of all participating hospitals and research institutes approved the study protocol, and all living subjects provided written informed consent.

## Data Collection

Trained research assistants completed a study data form for each cohort member. We recorded personal data, including name, date of birth, sex, and address at the time of treatment. If the date of birth was not given, the year of birth was calculated from the date of the first consultation and the subject's age at that time. We also recorded medical data, including the date of the first consultation, treatment status (NRI or nonexposed), and initial diagnosis. For NRI-exposed subjects, both the date and the duration of each treatment session were recorded. In addition, we collected information on the standard treatment protocols and characteristics of the radium applicators in every clinic (*see below*).

## Follow-up

An attempt was made to collect complete vital status information for each cohort member from the date of first ENT treatment until the date of death, emigration, or closure to the study (September 15, 1997). For subjects from the original cohort, the vital status as of February 1, 1985, was already available. However, for subjects in the expanded cohort, the vital status had to be retrieved based on the names and (mainly childhood) addresses listed in the medical records. Vital status and current address of cohort members were ascertained through information provided by the municipal population registries. These registries keep highly accurate records of the Dutch population and are, therefore, commonly used for follow-up studies (22).

We sent a letter requesting information on the vital status of each cohort member to the population office of the last known municipality of residence. If a cohort member had died, the date, the place of death, and the death certificate number were recorded. If a cohort member had moved, the inquiry proceeded to the new municipality. This procedure was repeated until the vital status of the cohort member as of September 15, 1997, was confirmed. If a cohort member had emigrated, we contacted a special bureau of the Dutch Ministry of Foreign Affairs that keeps records of persons who move abroad and registers the new place of residence in case they return to The Netherlands. We could not obtain the vital status for a small number of cohort members who were considered to be lost to follow-up because

either they were unknown in the municipality listed on the medical record or they had left their hometown without notifying the municipality. For these cohort members, a final search request was sent to the Central Bureau of Genealogy, a nationwide registry of deceased Dutch citizens, in which records are indexed only by name and year of death.

Information was obtained from Statistics Netherlands on the cause of death for each deceased cohort member. All causes of death in The Netherlands are coded by trained nosologists at Statistics Netherlands who use the International Classification of Diseases (23) applicable to the particular calendar period. For this study, all registered causes of death that used earlier revisions were recoded according to the 9<sup>th</sup> revision.

Among the eligible 5392 NRI-exposed subjects, 34 were excluded because of incomplete NRI treatment data ( $n = 23$ ) or unknown sex or date of birth ( $n = 11$ ). Among the eligible 5301 nonexposed subjects, 36 were excluded because of the uncertainty about treatment status ( $n = 5$ ), duplication in the cohort ( $n = 5$ ), unknown sex or date of birth ( $n = 9$ ), or unknown date of first treatment ( $n = 17$ ). Thus, this study analyzed data from 5358 NRI-exposed subjects and 5265 nonexposed subjects, with complete data on all relevant variables. The cohort included 57% males. Eighty percent of the cohort members were born from 1940 through 1970. Fifty-two percent of NRI-exposed subjects had their first radiation treatment between the ages of 5 and 9 years, 21% were treated before the age of 5 years, and 11% were treated after the age of 19 years. The median follow-up was 31.6 years.

## Dosimetry

An NRI treatment typically consisted of one to four daily sessions, usually separated by intervals of 1 week, depending on the clinic's standard treatment protocol. A session consisted of a single radium source inserted into the nasopharynx for 5–20 minutes. Fewer than 1% of all NRI-exposed subjects received more than one treatment.

For one clinic, sources were placed bilaterally; however, for the other clinics, the source was inserted in either the right or the left nostril and alternated on subsequent sessions, if any. A standard treatment sequence of right–left–right–left (used in the clinic where the majority of treatments took place) was assumed for NRI-exposed subjects for whom laterality was unknown. Total radium exposure was measured in total milligram-hours (mgh), the product of the radium source activity and treatment duration (6) (range, 3–74 mgh; mean, 18.2 mgh). Because measurements of organ doses during the treatments were not available, the absorbed radiation doses to various organs (i.e., head and neck area and breast) had to be calculated on the basis of measurements in anthropomorphic phantoms.

Most applicators contained radium within a Monel filter, a nickel alloy, of 0.1–0.3 mm in thickness. Sources with Monel filters are now obsolete and were not available for testing; however, the dose distribution up to 10 cm from a Monel-filtered source was published by Verduijn (9). The dose distribution from a platinum-filtered radium source measured in a tissue-equivalent phantom (24) showed that a Monel-filtered source resulted in doses that were approximately 15% higher. The Monel dose distribution was used to estimate the

dose to organs up to 10 cm from the source; at greater distances, the organ doses were estimated by increasing the absorbed dose from a platinum-filtered source by 15%. These data were applied to all patients, although the filter material and thickness were known only for the clinics included in the earlier study (9).

Absorbed doses to the organs of interest were calculated by use of the distance from the nasopharynx to each organ for children of various ages (25). We assumed that the nasopharyngeal cavity was 2.0 cm in diameter, regardless of age, and that the radium applicator was placed in the center of each side of the cavity (9). To calculate the absorbed dose to the brain, we estimated the radiation dose for multiple anatomic subsites for each subject. Both the average and the maximum dose to these subsites within each individual were treated as representative of the dose to the brain for that subject. Total active bone marrow (ABM) doses were calculated by use of the age-specific proportional distributions of ABM published by Christy (26).

## Statistical Analysis

Person-years at risk were calculated from the date of first NRI treatment for NRI-exposed subjects or the date of first consultation for nonexposed subjects, until the date of death, emigration, loss to follow-up, or end of follow-up (September 15, 1997). For a subgroup of 237 NRI-exposed subjects at one specific clinic (*see* "Study Population"), the date of entry in the study was fixed at January 1, 1982.

For comparison with the Dutch general population, the numbers of deaths observed (O) in both the NRI-exposed and nonexposed subject groups were compared with the numbers of deaths expected (E). To calculate the expected numbers of deaths, person-years were multiplied by the appropriate sex-, age-, and calendar period-specific reference death rates from 1950 through 1997 for the general population (Department of Population, Statistics Netherlands) and summed. Data were stratified by calendar period of follow-up (1940–1949, 1950–1959, 1960–1969, 1970–1979, 1980–1989, and 1990–1997), sex, attained age (0–4, 5–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and  $\geq 80$  years), treatment prescription dose (nonexposed,  $<10$ , 10–19, 20–29, 30–39, and  $\geq 40$  mgh), age at first treatment (0–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, and  $\geq 50$  years), and clinic. For each cell of the aggregated data file, the number of person-years and the number of observed and expected deaths were calculated. In addition, the number of person-year weighted averages of attained age, age at first treatment, and organ-specific radiation doses were calculated.

Standardized mortality ratios (SMRs, defined as the O/E ratio) were obtained, and likelihood ratio based 95% confidence intervals (CIs) were calculated under Poisson assumptions for the observed frequencies (27,28). SMR analyses were performed for all-cause mortality, major disease categories, and cancer-specific mortality, particularly for cancers of the head and neck area, breast, female genital tract, and prostate and for malignancies of hematopoietic and lymphoproliferative origin. Among NRI-exposed subjects, analyses were stratified by follow-up period, age at first treatment, and treatment prescription dose for selected tumor sites. Trend tests for SMR were performed as described by Breslow and Day (28).

Relative risk (RR) analyses used Poisson regression with cell-specific observed values and cell-specific expected frequency instead of person-years (29). That is, for each cell, the observed frequency was assumed to correspond to a Poisson variable, with a mean equal to the expected frequency of the population (E), treated as known, times a parametric function that depended on exposure or estimated radiation dose (D). Thus, the model for comparing nonexposed subjects and NRI-exposed subjects was mean (O) =  $\alpha E$  for nonexposed subjects and  $\alpha(1 + \beta E)$  for NRI-exposed subjects, where  $\alpha$  and  $\beta$  are unknown parameters,  $RR = 1 + \beta$ , and the excess RR (ERR) =  $\beta$ . For radiation dose-specific comparisons, the linear model is mean (O) =  $\alpha(1 + \gamma D)$ , where  $\gamma D$  = the ERR at dose D and the unknown parameter  $\gamma$  = ERR per unit dose. Finally, a general model was used in which an effect of exposure *per se* was combined with a linear dose-response among the exposed: mean (O) =  $\alpha(1 + \beta E)(1 + \gamma D)$ . All statistical tests were two-sided.

## RESULTS

Mortality was compared between NRI-exposed and nonexposed subjects in a Dutch cohort of patients. In all, tracing was completed for 92% of the cohort, regardless of exposure status. Death certificates were available for all but two deceased subjects. The median attained age of those alive in 1997 was 41 years (range, 18–87 years).

Estimates of absorbed doses for several organs associated with NRI are listed in Table 1. Tissues in close vicinity of the radium capsule during treatment received radiation doses ranging from 32 cGy to greater than 1000 cGy. The estimated average radiation doses to other organs in the head and neck area were less than 20 cGy, although in 12% of the NRI-exposed subjects, the dose to the pituitary gland exceeded this level. The estimated maximum dose to the brain was greater than

20 cGy in 8% of the NRI-exposed subjects; however, the estimated average dose to the brain was less than 10 cGy in all of the NRI-exposed subjects. The radiation dose to the thyroid was less than 5 cGy in 96% of the NRI-exposed subjects. The estimated average dose to the female breast was 0.1 cGy but was less than 1 cGy in even the most heavily exposed subjects.

The number of deaths in each disease category is shown in Table 2. We observed a total of 617 deaths in the cohort treated in ENT clinics 16–49 years earlier. A total of 302 NRI-exposed subjects had died of all causes in the 158 159 person-years of follow-up, with an SMR of 1.1 (95% CI = 1.0 to 1.3). The most common specific causes of death for NRI-exposed subjects were malignant diseases (O = 96 deaths; SMR = 1.2; 95% CI = 0.95 to 1.4) and disorders of the circulatory system (O = 87 deaths; SMR = 1.1; 95% CI = 0.9 to 1.4). None of the SMRs among NRI-exposed subjects were statistically significant (Table 2). A total of 315 nonexposed subjects had died of all causes (SMR = 1.1; 95% CI = 0.99 to 1.2). The most common specific causes of death were malignant diseases (O = 87 deaths; SMR = 1.0; 95% CI = 0.8 to 1.3) and disorders of the circulatory system (O = 73 deaths; SMR = 0.9; 95% CI = 0.7 to 1.2). The SMRs for disorders of the central nervous system (SMR = 2.1; 95% CI = 1.2 to 3.5) and the respiratory system (SMR = 2.3; 95% CI = 1.5 to 3.3) were statistically significant. Although the SMRs were elevated for congenital abnormalities (SMR = 1.8; 95% CI = 0.8 to 3.5) and for disorders of the endocrine and metabolic system (SMR = 1.8; 95% CI = 0.98 to 3.0), the increases were not statistically significant. For all other disease categories, the number of deaths observed was not more than expected or the comparisons were based on very small numbers of deaths.

We next analyzed the data according to specific cancer sites. Five NRI-exposed subjects died of malignant cancers of the head and neck area (SMR = 0.9; 95% CI = 0.3 to 2.2), and seven nonexposed subjects died of such cancers (SMR = 1.3; 95% CI = 0.5 to 2.6) (Table 3). Two additional NRI-exposed subjects died of brain tumors that could not be classified as benign or malignant because of a lack of diagnostic information. All NRI-exposed subjects who died of cancers in the head and neck area had been treated

with NRI after the age of 40 years, and two deaths occurred within 10 years of NRI treatment. No deaths from thyroid cancer were noted.

We noted more deaths from malignancies of lymphoproliferative and hematopoietic origin than expected (O = 17 deaths; SMR = 1.9; 95% CI = 1.1 to 3.0) among NRI-exposed subjects (Table 3). This increase mainly reflected seven deaths from non-Hodgkin's lymphoma (NHL) (SMR = 2.6; 95% CI = 1.0 to 5.3). Also, there were three deaths from multiple myeloma (SMR = 2.8; 95% CI = 0.6 to 8.1) and seven deaths from leukemia (SMR = 1.6; 95% CI = 0.7 to 3.4). Among nonexposed subjects, slightly fewer deaths from malignancies of lymphoproliferative and hematopoietic origin were observed than expected (O = six deaths; SMR = 0.6; 95% CI = 0.2 to 1.4). Compared with nonexposed subjects, the RR for NRI-exposed subjects was 3.0 (95% CI = 1.3 to 8.3) for malignancies of lymphoproliferative and hematopoietic origin (Table 3). A dose-response analysis, which included the nonexposed subjects, showed a statistically significant effect of ABM dose (ERR/cGy = 4.5; 95% CI = 0.5 to 16.9). However, after adjustment for the effect of exposure *per se*, the dose-response relationship could no longer be demonstrated.

Among hormone-related cancers potentially associated with pituitary radiation dose (21), there were more breast cancer deaths than expected (O = 13, SMR = 1.7, and 95% CI = 0.9 to 2.8 in 68 213 woman-years of follow-up). No statistically significant association was found between breast cancer mortality and dose to the breast (ERR/cGy = 7.2; 95% CI = -0.9 to 27.4) or to the pituitary (ERR/cGy = 0.07; 95% CI = -0.009 to 0.28) (data not shown). The number of deaths from cancers of the female genital tract was small (O = 4; SMR = 1.1; 95% CI = 0.3 to 2.8) and close to the expected number of deaths (Table 3). Only two prostate cancer deaths (one exposed subject and one nonexposed subject) were observed among males.

We also assessed the possible effects of treatment prescription dose, age at treatment, and time since treatment on the SMR among NRI-exposed subjects (Table 4). For malignancies of lymphoproliferative and hematopoietic origin, SMRs were increased for all prescription-dose categories, except one (10–19 mgh),

**Table 1.** Overview of estimated organ doses in The Netherlands nasopharyngeal radium irradiation cohort

| Organ           | Dose, cGy |         |         |
|-----------------|-----------|---------|---------|
|                 | Mean      | Minimum | Maximum |
| Nasopharynx     | 275       | 32      | 1110    |
| Base of tongue  | 20.7      | 2       | 130     |
| Pituitary       | 10.9      | 1       | 59      |
| Parotid gland   | 7.0       | 1       | 28      |
| Brain, maximum* | 9.1       | 1       | 37      |
| Brain, average† | 1.8       | 0.3     | 8       |
| Thyroid         | 1.5       | 0.2     | 11      |
| Total ABM‡      | 0.4       | 0       | 3       |
| Breast          | 0.1       | 0       | 0.9     |

\*Maximum dose to 282 points throughout the brain.

†Average dose to 282 points throughout the brain.

‡ABM = active bone marrow.

**Table 2.** Mortality from major diseases in The Netherlands nasopharyngeal radium irradiation (NRI) cohort, by exposure status

| Cause of death                           | ICD-9*  | NRI-exposed subjects (158 159 PY)† |       |                   | Nonexposed subjects (163 756 PY) |       |                   |
|--|---------|------------------------------------|-------|-------------------|----------------------------------|-------|-------------------|
|  |         | O                                  | E     | SMR (95% CI)      | O                                | E     | SMR (95% CI)      |
| All causes                               |         | 302                                | 269.2 | 1.1 (1.0 to 1.3)  | 315                              | 283.5 | 1.1 (0.99 to 1.2) |
| Malignant disease                        | 140–208 | 96                                 | 82.2  | 1.2 (0.95 to 1.4) | 87                               | 86.0  | 1.0 (0.8 to 1.3)  |
| Endocrine, metabolic, and immune systems | 240–279 | 7                                  | 7.6   | 0.9 (0.4 to 1.9)  | 14                               | 7.8   | 1.8 (0.98 to 3.0) |
| Central nervous system                   | 320–349 | 4                                  | 7.0   | 0.6 (0.2 to 1.5)  | 16                               | 7.5   | 2.1 (1.2 to 3.5)  |
| Circulatory system                       | 390–459 | 87                                 | 77.0  | 1.1 (0.9 to 1.4)  | 73                               | 80.1  | 0.9 (0.7 to 1.2)  |
| Respiratory system                       | 460–519 | 12                                 | 11.5  | 1.0 (0.5 to 1.8)  | 28                               | 12.3  | 2.3 (1.5 to 3.3)  |
| Digestive system                         | 520–579 | 14                                 | 8.6   | 1.6 (0.9 to 2.7)  | 12                               | 9.1   | 1.3 (0.7 to 2.3)  |
| Congenital abnormalities                 | 740–759 | 2                                  | 3.4   | 0.6 (0.07 to 2.2) | 8                                | 4.5   | 1.8 (0.8 to 3.5)  |

\*International Classification of Diseases, 9<sup>th</sup> Revision (23).

†PY = person-years; O = observed number of deaths, E = expected number of deaths; SMR = standardized mortality ratio, defined as O/E; CI = confidence interval.

**Table 3.** Cancer-specific mortality in The Netherlands nasopharyngeal radium irradiation (NRI) cohort, by exposure status

| Cancer-specific cause of death        | NRI-exposed group (158 159 PY)* |                   | Nonexposed group (163 756 PY)* |                   | RR (radium), RR (95% CI)† |
|---------------------------------------|---------------------------------|-------------------|--------------------------------|-------------------|---------------------------|
|                                       | O                               | SMR (95% CI)†     | O                              | SMR (95% CI)†     |                           |
| Head and neck area‡                   | 5                               | 0.9 (0.3 to 2.2)  | 7                              | 1.3 (0.5 to 2.6)  | 0.7 (0.2 to 2.3)          |
| Brain§                                | 2                               | 0.6 (0.1 to 2.1)  | 5                              | 1.4 (0.5 to 3.2)  | 0.4 (0.1 to 1.9)          |
| Thyroid                               | 0                               | (0.0 to 17.2)     | 0                              | (0.0 to 16.8)     | —                         |
| Oral cavity and pharynx               | 2                               | 1.8 (0.2 to 6.4)  | 0                              | (0.0 to 3.4)      | —                         |
| Larynx                                | 1                               | 1.8 (0.1 to 10.1) | 2                              | 3.6 (0.4 to 12.9) | 0.5 (0.02 to 5.3)         |
| Lymphoproliferative and hematopoietic | 17                              | 1.9 (1.1 to 3.0)  | 6                              | 0.6 (0.2 to 1.4)  | 3.0 (1.2 to 8.3)          |
| Non-Hodgkin's lymphoma                | 7                               | 2.6 (1.0 to 5.3)  | 2                              | 0.7 (0.7 to 2.6)  | 3.6 (0.9 to 24.4)         |
| Hodgkin's disease                     | 0                               | (0.0 to 3.4)      | 0                              | (0.0 to 3.4)      | —                         |
| Multiple myeloma                      | 3                               | 2.8 (0.6 to 8.1)  | 0                              | (0.0 to 3.4)      | —                         |
| Leukemia                              | 7                               | 1.6 (0.7 to 3.4)  | 4                              | 0.9 (0.2 to 2.3)  | 1.9 (0.6 to 7.2)          |
| Breast                                | 13                              | 1.7 (0.9 to 2.8)  | 9                              | 1.1 (0.5 to 2.0)  | 1.6 (0.7 to 3.8)          |
| Female genital tract¶                 | 4                               | 1.1 (0.3 to 2.8)  | 6                              | 1.4 (0.5 to 3.1)  | 0.8 (0.2 to 2.7)          |
| Prostate                              | 1                               | 0.4 (0.01 to 2.2) | 1                              | 0.4 (0.01 to 2.2) | 1.0 (0.04 to 25.0)        |

\*Total number of person-years (PY). The number of PYs among NRI-treated females = 68 213; among non-NRI-treated females = 72 179.

†SMR = standardized mortality ratio, defined as O/E; O = observed number of deaths, E = expected number of deaths; CI = confidence interval; RR = relative risk.

‡Defined as International Classification of Diseases, 9<sup>th</sup> Revision (ICD-9) codes 140–149, 160, 161, 191, and 193.

§In addition, two deaths due to brain tumors of nonspecified behavior (ICD-9 code 239.6) were observed among exposed subjects, i.e., tumors that could not be defined “benign” or “malignant” because of a lack of diagnostic information; adding O and E to the brain tumor analyses rendered a combined SMR of 1.0.

||Subtypes of leukemia (number)—among exposed: acute lymphoblastic (one), chronic lymphoblastic (one), acute myelocytic (one), chronic myelocytic (two), subacute myelocytic (one), and unspecified (one); among nonexposed: acute myelocytic (one), acute erythrocyte (one), acute monocyte (one), and acute not otherwise specified (one).

¶Specific cancer sites (number)—among NRI-exposed subjects: cervix (one), uterus (one), and ovary (two); among nonexposed subjects: cervix (three), uterus (1), and ovary (two).

and were increased regardless of age at treatment, although not statistically significantly (Table 4). When the data were analyzed by time since treatment, there was a statistically significant trend ( $P = .02$ ) toward increasing SMR with longer follow-up, with SMRs of 2.7 (95% CI = 1.0 to 5.9) and 3.1 (95% CI = 1.4 to 6.2) in the intervals of 20–29 years and more than 30 years since treatment, respectively. Female subjects exposed to more than 30 mGy had nonstatistically signifi-

cantly elevated SMRs. Mortality from breast cancer was negatively, but nonstatistically significantly, associated with age at treatment, with the highest risk found among women treated with radium before 10 years of age. There was a slight, but nonstatistically significant trend ( $P = .15$ ) between the risk of breast cancer death and increasing time since treatment. Women who were followed for 30 years or more had an SMR of 2.3 (95% CI = 1.0 to 4.3).

## DISCUSSION

In this the largest cohort study of NRI-treated subjects to date, we found no association between NRI and subsequent mortality from cancers of the head and neck area, the thyroid, and the brain. Nasopharyngeal tissues adjacent to the radium capsule during treatment were exposed to the highest radiation doses. However, we and others (11,21) found no association between NRI and pharyngeal cancers. Hazen et al. (11) reported no pharyngeal cancers after 15 years of follow-up in 417 NRI-treated subjects and, although Sandler et al. (12) reported one pharyngeal cancer, an anaplastic soft-palate cancer, in 904 NRI-treated subjects, prolonged follow-up of this cohort revealed no additional pharyngeal cancers (21). It has been suggested that the local radiation dose in the nasopharyngeal cavity may have been sufficiently high (up to 11 Gy in our study) to induce cell death, which would preclude the generation of any malignancy (30).

We found no deaths from thyroid cancer perhaps because the extremely low dose of radiation to the thyroid (mean, 1.5 cGy) was not sufficient to induce an observable number of tumors. Alternatively, our study may have insufficient statistical power to detect such an association (31,32), because few fatal thyroid malignancies were expected (<1). Excess thyroid cancer risk has been described after exposure to doses as low as 10 cGy (33).

We found no more deaths from brain cancer than expected. Yeh et al. (21) reported a statistically nonsignificant RR of 14.8 (95% CI = 0.8 to 286.3) for brain cancers on the basis of the three deaths in their cohort and noted four benign brain tumors. However, the average radiation dose to the pituitary in their study (21) was estimated to be at least 78 cGy, which

**Table 4.** Mortality from selected cancers in radium-treated subjects of The Netherlands nasopharyngeal radium irradiation cohort, by treatment prescription dose, age at treatment, and time since treatment

| Stratification factor             | Person-years at risk | All cancers |                   | Cancers of lymphoproliferative and hematopoietic origin |                   | Breast cancer |                   |
|-----------------------------------|----------------------|-------------|-------------------|---|-------------------|---------------|-------------------|
|                                   |                      | O*          | SMR (95% CI)      | O   | SMR (95% CI)      | O             | SMR (95% CI)      |
| Treatment prescription dose, mgh† |                      |             |                   |   |                   |               |                   |
| <10                               | 7560                 | 5           | 1.2 (0.4 to 2.9)  | 1   | 2.2 (0.1 to 12.4) | 0             | (0.0 to 8.2)      |
| 10–19                             | 103 545              | 24          | 0.9 (0.5 to 1.3)  | 4   | 0.9 (0.3 to 2.4)  | 4             | 1.3 (0.4 to 3.4)  |
| 20–29                             | 17 224               | 42          | 1.3 (0.96 to 1.8) | 5   | 2.1 (0.7 to 4.8)  | 3             | 1.3 (0.3 to 3.9)  |
| 30–39                             | 16 661               | 15          | 1.3 (0.7 to 2.1)  | 5   | 4.2 (1.4 to 9.7)  | 4             | 2.7 (0.7 to 6.9)  |
| ≥40                               | 13 167               | 10          | 1.5 (0.7 to 2.7)  | 2   | 2.6 (0.3 to 9.4)  | 2             | 3.2 (0.4 to 11.5) |
| Age at treatment, y               |                      |             |                   |   |                   |               |                   |
| 0–9                               | 115 538              | 17          | 0.9 (0.5 to 1.5)  | 5   | 1.2 (0.4 to 2.9)  | 6             | 2.5 (0.9 to 5.4)  |
| 10–19                             | 27 143               | 10          | 0.9 (0.4 to 1.6)  | 5   | 3.6 (1.2 to 8.3)  | 3             | 1.6 (0.3 to 4.8)  |
| ≥20                               | 15 475               | 69          | 1.3 (1.0 to 1.7)  | 7   | 1.9 (0.8 to 2.9)  | 4             | 1.1 (0.3 to 2.9)  |
| Time since treatment, y           |                      |             |                   |   |                   |               |                   |
| 0–9                               | 49 762               | 10          | 1.0 (0.5 to 1.9)  | 1   | 0.5 (0.1 to 2.7)  | 0             | (0.0 to 5.9)      |
| 10–19                             | 47 972               | 14          | 0.8 (0.4 to 1.4)  | 2   | 0.9 (0.1 to 3.1)  | 1             | 0.8 (0.04 to 4.6) |
| 20–29                             | 36 653               | 31          | 1.4 (0.96 to 2.0) | 6   | 2.7 (1.0 to 5.9)  | 3             | 1.5 (0.3 to 4.2)  |
| ≥30                               | 23 771               | 41          | 1.2 (0.9 to 1.7)  | 8   | 3.1 (1.4 to 6.2)‡ | 9             | 2.3 (1.0 to 4.3)  |

\*O = observed number of deaths; SMR = standardized mortality ratio, defined as O/E, where E = expected number of deaths; CI = confidence interval.

†mgh = activity of radium source in milligrams (mg) × total duration of radiation treatment sessions in hours (h).

‡*P*<sub>trend</sub> = .02.

was much higher than the 11 cGy in our study. In the New York NRI cohort (11), only one brain cancer was observed among NRI-exposed subjects compared with two among nonexposed subjects. A follow-up study of 1214 NRI-treated and 3176 untreated adult submarine trainees during World War II (14) reported slightly elevated mortality from head and neck cancers as a group (RR = 1.4; 95% CI = 0.5 to 3.5), without further detail. Thus, evidence regarding brain cancer risk following NRI treatment is mixed and no definitive conclusions can be reached.

High-dose childhood radiation exposures in the head and neck area have been linked to elevated brain cancer risk (34,35). A study among 28 008 infants treated for skin hemangioma (36) reported an excess risk associated with radiation doses partly overlapping those experienced by subjects in our NRI cohort. The excess risk was inversely associated with the age at treatment, with the highest risk among those treated before the age of 5 months. Because the average age at treatment in our study was higher and the average dose to the brain was lower, the two studies are not necessarily inconsistent.

We noted more deaths from malignancies of lymphoproliferative and hematopoietic origin, which became evident more than 15 years after NRI treatment and mainly reflected an increase in the risk of fatal NHL. Elevated risks for NHL

or multiple myeloma were not reported in the U.S. NRI cohorts (11,21) or in studies of other types of childhood radiation treatments to the head and neck area (37–39). If any, the effect of low-dose radiation in the etiology of NHL and multiple myeloma is thought to be small or nonexistent (40,41). Thus, the possibility of a chance finding should also not be ruled out, since numbers were small and multiple statistical testing was done. Furthermore, with regard to a possible dose-response relationship, our data were statistically just as consistent with an effect of exposure *per se* as with a linear effect of dose. In NRI treatment, lymphoid tissues in the nasopharynx receive the highest radiation doses. Unfortunately, the available data on death certificates precluded our analysis of NHL site-specific mortality.

Leukemia has been associated with radiation exposure (40). Increased risk of death from leukemia could be detected among atomic-bomb survivors exposed to greater than 20 cGy (total ABM dose) (42) and among young adults exposed to head and neck irradiation for tinea capitis during childhood (37). In both of the studies (37,42), the peak incidences of leukemia were reached within 10 years after radiation exposure. The total ABM dose in our study was only 0.4 cGy, and the slight increased risk was not observed until 20 years after the NRI treatment. Consequently, it is questionable if our elevated SMRs for malignancies of hema-

topoietic and lymphoproliferative origin are due to radiation.

Yeh et al. (21) reported a decreased risk for a combined group of hormone-related cancers (breast, ovarian, endometrial, and prostate) in a cohort of 914 NRI-exposed subjects and hypothesized a possible association between the NRI radiation dose and the pituitary. In our study, no evidence of decreased mortality from breast or female genital tract cancers was found. If at all, cancer-specific mortality appeared to increase with increasing doses of radiation to the pituitary. One of many possible explanations for the discrepancy between our results and those of the Maryland cohort (21) might be that the average radiation dose to the pituitary in the latter study was much higher than that in our cohort.

The strengths of our study design are as follows: Data on individual radiation treatments were verified, and a fair range of radiation exposures was established. We also identified an internal reference group to ensure unbiased comparisons because ENT patients might have a different pattern of disease occurrence than the general population. Analyses revealed, however, that nonexposed subjects had increased mortality from respiratory diseases and central nervous system disorders. These patterns may be related to the diagnosis at first consultation at the ENT clinic because the majority of NRI-exposed subjects (92%) were referred with recurrent (serous) otitis compared

with only 36% of nonexposed subjects. By contrast, almost 20% of the nonexposed subjects were referred for diverse reasons, representing a wide variety of ENT symptoms related to systemic disorders with complications in the ENT area compared with fewer than 1% of the exposed subjects. Because the median attained age of the cohort was only just above 40 years, the expected numbers of site-specific cancer deaths were generally small. The statistical power of our study was sufficient to detect a 2.5-fold increase in the risk of death from a cancer of the head and neck area with 80% probability (28).

In summary, this report on a Dutch cohort of NRI-treated patients did not reveal strongly increased risks for mortality from cancer. Our analysis of cancer incidence in this cohort is under way, which should provide a more thorough evaluation for cancers with good prognosis and for the incorporation of confounding factors in the analysis. Within 10–15 years from now, the majority of the NRI-exposed subjects will be between 40 and 60 years of age, and the underlying risk of cancer will rise substantially in accord with the risk of cancer for the general population. More specific analyses of the patterns of cancer-specific deaths will then be feasible. Any definitive conclusions regarding the risk of cancer associated with NRI must await further prolonged follow-up.

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## NOTES

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